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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,194	09/17/2001	Mark E. Gurney	29915/6177PCP	3788

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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 11/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,194	GURNEY ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *151-300* is/are pending in the application.

4a) Of the above claim(s) *151-231,241-271 and 279-300* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *232-240 and 270-278* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *151-300* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election **with** traverse of Group 15 (claims 232-240, 270-272, and 274-278) drawn to APP proteins, polynucleotides, vectors, and host cells comprising same in the Response filed 4 September 2003 is acknowledged. The traversal is on the ground(s): (a) the USPTO must follow the determination of unity as set forth by the EPO in the IPER and (b) claims 232-240 and 270-278 share a special technical feature.

2. This is not found persuasive because the USPTO is not bound by any decision made during the PCT stage of the instant application. At each and every stage of the PCT application decisions are made concerning lack of unity, including the final national entry stage pursuant to 35 U.S.C. 371. The PCT reports (International Search Report, Written Opinion, and International Preliminary Examination Report) are all considered advisory actions and are not binding on the national office during the national stage (MPEP §1875, §1893.03). On "(b)" as set forth in the Restriction Requirement (4 March 2003), the claims as presented do not share a special technical feature.

3. However, as a courtesy to the Applicant and in the interest of compact prosecution (MPEP §707) the Examiner hereby rejoins Groups 15, 16, and 17 drawn to SEQ ID NO: 18, 19, and 20. Claims **151-231, 241-269,** and **279-300** are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the Response filed 4 September 2003. The requirement is still deemed proper and is therefore made FINAL.

4. It is noted by the Examiner that the Restriction Requirement mailed 4 March 2003 was performed under lack of unity practice pursuant to MPEP §1893.03.

Status of Application, Amendments, and/or Claims

5. The Response and Amendment filed 4 September 2003 has been received and entered in full. Claims 1-150 have been cancelled and claims 151-300 are currently pending.

Specification

6. The disclosure is objected to because of the following informalities: "A□" (pp. 45 lines 1-25). Appropriate correction is required.

Claim Objections

7. Claim **239** is objected to because of the following informalities: claim 239 depends from claim 86, an unelected claims. Appropriate correction is required.

Double Patenting

> The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
>
> A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims **232-240** and **270-278** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11-19 of U.S. Patent No. 6,440,698 B1 (27 August 2002) Gurney *et al.* Although the conflicting claims are not identical, they are not patentably distinct from each other because US 6440698 claims a host cell transfected with a nucleic acid comprising a nucleotide sequence that encodes an amyloid precursor protein (APP) or fragment thereof containing a β-secretase cleavage site. US 6440698 also claims a host cell wherein said APP includes two-carboxyl-terminal lysine residues, wherein said APP comprises the Swedish mutation (K→N, M→L), and furthermore, wherein the polypeptides of said host cell are purified. In addition, US 6440698 offers definitions of host cells as, including but not limited to, HEK293 and Neuro2a as well as polypeptides that share 100% homology to SEQ ID NO: 16, 18, and 20 as APP's with double lysine resides at the C-terminus (sequence listing and Col. 7 lines 40-45).

9. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include the invention as claimed as to be a species of the genus claimed in US 6440698.

10. Thus the invention as a whole was *prima facia* obvious over US 6440698.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims **232-240** and **270-278** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *human isoforms of APP695 which end in two consecutive lysine residues at the C-terminus, including but not limited to SEQ ID NO: 16, 18, and 20*, does not reasonably provide enablement for *any given isoform of APP which end in two consecutive lysine residues at the C-terminus*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make or use** the invention commensurate in scope with these claims.

12. The claims are drawn very broadly to any APP isoform or fragment thereof that has two consecutive lysine residues at its C-terminal end [see Haas *et al.* (1997) "Proteolysis of Alzheimer's disease β-amyloid precursor protein by factor Xa." Biochimica et Biophysica Acta **1343**(1): 85-94]. The language of said claims encompasses almost any sequence which shares almost any degree of similarity to APP, as well as at least 10 known mammalian species [Johnstone *et al.* (1991) "Conservation of the sequence of the Alzheimer's disease amyloid peptide in dog, polar bear and five other mammals by cross-species polymerase chain reaction analysis." Molecular Brain Research **10**: 299-305]. According to Ghiso *et al.* (1992) "A 109-amino-acid C-terminal fragment of Alzheimer's-disease amyloid precursor protein contains a sequence, -RHDS-, that promotes cell adhesion." Biochem. J. **288**(3): 1053-1059 teach that APP has four known major isoforms (APP_{695}, APP_{714}, APP_{751}, APP_{770}). The claims as written read on all of these known isoforms and as of yet unknown or uncharacterized isoforms of APP.

13. The specification teaches that amyloid precursor-protein (APP) is found in several forms including a 771, 770, and 695 length and usually does not end in two consecutive lysine residues

at the C-terminus. In addition the Specification teaches the Swedish and London mutations for APP are both involved in Alzheimer's disease.

14. The specification fails to provide any guidance for the successful isolation and characterization of any isoform of APP except for APP_{695}, and since resolution of the various complications in the protein biochemistry of isoforms of APP is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations with known isoforms of APP to predict, isolate, and characterize a multitude of isoforms besides the APP_{695} derivatives taught in the Specification. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed as it represents an invitation to experiment [see Ohgami *et al.* (1993) "The Rat Central Nervous System Expresses Alzheimer's Amyloid Precursor Protein APP695, but Not APP677 (L-APP Form)." Journal of Neurochemistry **61**(4): 1553-1556].

15. Additionally, a person skilled in the art would recognize that predicting the efficacy of making any number of APP derivatives, mutants, and variants based solely on the data from a single isoform as highly problematic (see MPEP §2164.03). Thus, although the specification prophetically considers and discloses general methodologies of making known and unknown APP derivatives with two consecutive lysine residues at the C-terminus, such a disclosure would not be considered enabling since the state of APP protein biochemistry is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

16. The following references are cited herein to illustrate the state of the art of APP.

17. On the breadth of the claims, the claims only require that the undisclosed sequences be mammalian APP with two lysine residues at the carboxy-terminus, however, the prior art teaches that not all mammalian forms of APP are the same. For instance, Strooper *et al.* (1995) "Production of intracellular amyloid-containing fragments in hippocampal neurons expressing human amyloid precursor protein and protection against amyloidogenesis by subtle amino acid substitutions in the rodent sequence." The EMBO Journal 14(20): 4932-4938 teaches that minor amino acid substations radically altered the protease susceptibility of APP (Figure 5). Thus leaving the skilled artisan with an undue burden of experimentation with no guidance to determine whether or not the non-pathogenic forms of APP, or does the murine isoform, which is functionally different from the human isoform, satisfy the limitations of the claims.

18. On the nature of the invention, Yamada & Kobayashi (1995) "The mutation in amyloid precursor protein inhibits both α- and β-secretion." Neuroscience Letters **191**(1,2): 103-106 teach that a single amino acid change (Lys612Val) can eliminate proteolytic processing of APP (Figures 1 and 2). Thus in the absence of specific sequences or more limitations, it is not clear to

the skilled artisan as to which APP's fall within the claimed genus of "containing an APP cleavage site recognizable by a mammalian β-secretase".

19. On the level of predictability, the claims as written encompass a broad genus of APP isoforms. de Silva *et al.* (1997) "Cell-specific expression of β-amyloid precursor protein isoform mRNAs and proteins in neurons and astrocytes." Molecular Brain Research **47**(1,2): 147-156 teaches that APP exists in different splice variants depending upon cell type (pp. 154). Therefore a level of unpredictability exists whether any given isoform of APP will be susceptible to β-secretase or be a valid species of the genus claimed due to the heterogeneity of the distribution and assembly of the APP's.

20. On the state of the prior art, Citron *et al.* (March 1995) "Generation of Amyloid β protein from Its Precursor Is Sequence Specific." Neuron **14**(3): 661-670 teaches that the β-secretase cleavage site at the N-terminus of APP (Asp597) is not tolerant of amino acid changes. Therefore the skilled artisan is presented with the unpredictability of whether any given isoform, splice variant, species variants, and/or fragment will be susceptible to cleavage by a mammalian β-secretase. Thus not allowing a great variance in this critical region and presenting several species not eligible for the claimed genus.

21. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from a single isoform to any number of a multitude of known and unknown forms of APP as exemplified in the references herein.

22. Claims **232-240** and **270-278** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

23. The claims are drawn to APP isoforms having two consecutive lysine residues at the C-terminus. The claims do not require that the polypeptide possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claims are drawn to a genus of polypeptides that is defined by ending in two consecutive lysine residues.

24. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a recitation of membership to a large and diverse genus of proteins (APP). The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. The only adequately described species is a polypeptide comprising SEQ ID NO: 16, 18, 20, and human APP695. No active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus [see Johnstone *et al.* (1991) "Conservation of the sequence of the Alzheimer's disease amyloid peptide in dog, polar bear and five other mammals by cross-

species polymerase chain reaction analysis." Molecular Brain Research **10**: 299-305 and de Silva *et al.* (1997) "Cell-specific expression of β-amyloid precursor protein isoform mRNAs and proteins in neurons and astrocytes." Molecular Brain Research **47**(1,2): 147-156].

25. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

26. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

27. Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 16, 18, 20, and human APP695, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-*

Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

Summary

28. Claims **232-240** and **270-278** are hereby rejected.

29. The following articles, patents, and published patent applications were found by the Examiner during the art search while not relied upon are considered pertinent to the instant application:

a. US 6,500,667 B1 (31 December 2002) Gurney *et al.*

b. US 6,420,534 B1 (16 July 2002) Gurney *et al.*

c. US 5,604,131 (1997) Wadsworth *et al.*

d. US 5,455,169 (1995) Mullan

e. US 5,605,811 (1997) Seubert *et al.*

f. US 5,703,209 (30 December 1997) Vitek *et al.*

g. US 5,652,092 (29 July 1997) Vitek *et al.*

h. Usami *et al.* (July 1993) "The triplet of lysine residues (Lys724-Lys725-Lys726) of Alzheimer's amyloid precursor protein plays an important role in membrane anchorage and processing." J Neurochem **61**(1): 239-246

i. Moir *et al.* (27 February 1998) "Relative Increase in Alzheimer's Disease of Soluble Forms of Cerebral Aβ Amyloid Protein Precursor Containing the Kunitz Protease Inhibitory Domain." The Journal of Biological Chemistry **273**(9): 5013-5019

j. Yamatsuji *et al.* (1996) "Expression of V642 APP mutant causes cellular apoptosis as Alzheimer trait-linked phenotype." The EMBO Journal **15**(3): 498-509

k. Fraser *et al.* (18 November 1994) "Conformation and Fibrillogenesis of Alzheimer Aβ Peptides with Selected Substitution of Charged Residues." J. Mol. Biol. **244**(1): 64-73

l. Löffler *et al.* (1994) "Accumulation of a 50 kDa N-terminal fragment of β-APP_{695} in Alzheimer's Disease Hippocampus and Neocortex." Neurochem. Int. **24**(3): 281-288

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C Kennedy

CJN
November 3, 2003